IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of

PEPYS

Application Serial No.: 09/985,699

Filed: November 5, 2001

Title: THERAPEUTIC AGENT

Group Art Unit: 1654

Examiner: MELLER, M.V.

DECLARATION OF PROFESSOR MARK B. PEPYS PURSUANT TO 37 C.F.R. §1.132

I, Mark B. Pepys, hereby declare as follows:

(1) I am Professor of Medicine and Head, Department of Medicine, Hampstead Campus, Royal Free and University College Medical School, London, U.K. Further details of my educational qualifications and a list of publications are set out on the attached curriculum vitae (see Appendix A).

(2) I have worked in the field of chemical, biological, and clinical investigation of serum amyloid P component (SAP) for 30 years.

(3) I am the sole inventor of U.S. Patent Application No. 09/985,699, entitled "Therapeutic Agents" ("the '699 application").

(4) I have invented a method for depleting disease-associated proteins from the plasma of a subject in need of such treatment, which comprises administering to the subject a therapeutically effective amount of a non-proteinaceous agent that comprises a plurality of ligands covalently co-linked to permit complexation with a plurality of the disease-associated proteins, wherein at least two of the ligands are capable of being bound by ligand binding sites present on the proteins, and monitoring the clearance of the disease-associated proteins from the subject's plasma. In the claimed embodiments of my invention elected for examination in the '699 application, the non-proteinaceous agent is (R)-1-[6-(R)-2-Carboxypyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid or a pharmaceutically acceptable salt or

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mono- or diester thereof, and the disease-associated protein is serum amyloid P component (SAP). Prior to my present invention, there was no precedent for a small molecule drug that specifically targets a circulating plasma protein and causes its very rapid and profound clearance and depletion from the circulation. There is no prior art of any type that even remotely suggested this completely novel mechanism of drug action.

(5) I have read and am familiar with the official action issued by the U.S. Patent and Trademark Office and dated February 18, 2005, in connection with the '699 application.

(6) I have also reviewed both of the references cited by the examiner, *i.e.*, Hertel *et al.* (U.S. Patent No. 6,103,910) and van Kessel *et al* (U.S. Patent No. 6,365,570).

(7) I make this declaration in response to the official action issued February 18, 2005, in which the claims pending in the '699 application were rejected under 35 U.S.C. §103(a) because the claimed invention allegedly would have been obvious to a person of ordinary skill in the art at the time the invention was made, in view of Hertel et al., taken with van Kessel et al. The examiner stated that Hertel et al. taught administering (R)-1-[6-(R)-2-Carboxypyrrolidin-l-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid (the elected agent) to a patient in order to treat diseases associated with amyloidosis such as Alzheimer's disease. The examiner stated that "the compounds administered are used to prevent the interaction of SAP with amyloid fibrils," and acknowledged that Hertel et al. did not teach monitoring the clearance of SAP from the patient's plasma. However, the examiner alleged that it would have been obvious to monitor the clearance of SAP from the patient's plasma, because van Kessel et al. taught quantification of the concentration of SAP. See pages 3-4 of the official action.

(8) I strongly disagree with the examiner's conclusion that a person of ordinary skill in the art of developing and using treatments for diseases associated with amyloidosis would have been motivated by the cited references to perform the method of the claims pending in the '699 application, or would have held a reasonable expectation that the claimed method would operate successfully. My reasons for reaching this conclusion are explained below.

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(9) I disagree with the conclusion reached by the examiner that "Hertel teaches to administer the claimed compound of claim 20 (the elected agent) to a patient for treating diseases associated with amyloidosis such as Alzheimer's disease." This is wholly incorrect. Hertel does not describe the administration of any specific compound to a patient. Hertel et al. is concerned with identifying D-proline derivatives defined according to general formulas I-A or I-B (column 1, lines 30 to 45) that are potentially useful for treating diseases associated with amyloidosis, such as Alzheimer's disease. Formulas I-A and I-B are limited only by the identity of the functional groups as set out in the section bridging column 1 to column 2, line 48, and include a very large number of different compounds. A list of compounds is presented in columns 5 and 6, and later there are presented 104 different examples of the synthesis of specific compounds according to formulas I-A and I-B. Hertel et al. teaches that D-proline derivatives of formulas I-A or I-B that interfere with the binding of SAP to amyloid fibrils are potentially useful for therapy of amyloidosis and amyloidosis-associated diseases. This is taught by statements in the reference such as:

> "For therapy pharmaceutically active compounds have to be found which would prevent the interaction of SAP with amyloid fibrils" (col. 4, lines 27 to 29);

and

> "The participation of SAP in the pathogenesis of amyloidosis *in vivo* confirms that inhibition of binding to amyloid fibrils is an attractive therapeutic target in a range of serious human diseases" (col. 4, lines 39 to 42).

Moreover, Hertel et al. expressly teaches testing D-proline derivatives of formulas I-A or I-B for their ability to interfere with the binding of SAP to amyloid fibrils (columns 39-40, lines 55-67), and states that preferred compounds of formulas I-A and I-B inhibit the binding of SAP to amyloid fibrils with an IC_{50} value in the range of about 0.2 to 2.0 μM (col. 41, lines 1-2). One of ordinary skill in the art would not reasonably have regarded Hertel et al. as teaching that all of the disclosed D-proline compounds found to be capable of inhibiting the binding of SAP to amyloid fibrils can be used for therapy of amyloidosis and diseases that are associated with amyloidosis. The therapeutic efficacy of such compounds could only be determined through suitable *in vivo* trials. Hertel does not teach the skilled reader anything further about the administration of the disclosed D-prolines, because the reference describes no distinctions between the disclosed compounds, and no *in vivo* experiments or trials are described. Nothing is taught about the therapeutic efficacy of the compounds *in vivo*.

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Persons of ordinary skill in the art would therefore have regarded Hertel et al. as providing an invitation to perform *in vivo* tests of the disclosed compounds that inhibit the binding of SAP to amyloid fibrils, in order to determine which ones might be used for treating diseases associated with amyloidosis.

(10) My invention does not involve in any way the direct inhibition of SAP binding to amyloid fibrils, as required in Hertel et al. The method to which the claims pending in the '699 application are directed is based on my discovery that a palindromic or multi-ligand D-proline compound such as (R)-1-[6-(R)-2-Carboxypyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid (the elected agent) is capable of cross-linking pairs of SAP molecules to form complexes that are recognized as abnormal by a patient and are cleared from the patient's blood, as demonstrated by measurement of serum or plasma SAP concentration, to provide a therapeutic benefit. Clearance of SAP molecules from a patient's blood or plasma is neither measured nor predicted by Hertel et al., and there is no suggestion in Hertel et al. that a D-proline derivative of formula I-A or I-B that inhibits the interaction between the SAP and amyloid fibrils would successfully effect clearance of SAP molecules from the blood or plasma of a patient.

(11) Hertel et al. teaches that SAP is extremely stable outside the liver (column 4, line 38). This would have suggested to one of ordinary skill in the art that SAP would be likely to persist in blood or plasma, rather than be depleted from a patient's blood or plasma as is effected by the claimed invention.

(12) In summary, one of ordinary skill in the art would have regarded Hertel et al. as providing a suggestion to screen the disclosed D-prolines to identify compounds that inhibit the binding of SAP to amyloid fibrils, and to perform further assays to identify such compounds that are useful for treating amyloidosis and amyloidosis-associated diseases. However, Hertel et al. does not describe any experiments in which the disclosed D-proline compounds are administered to a subject, nor does the reference describe or suggest that a D-proline compound useful for therapy of amyloidosis and associated diseases might be capable of effecting clearance of SAP from a patient's blood or plasma. Hertel et al. therefore could

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not have suggested to one of ordinary skill in the art the claimed method which comprises actively monitoring the clearance of SAP from a patient's plasma.

(13) Van Kessel et al. describe possible uses of SAP and fragments of SAP totally unrelated to anything in my invention. I do not believe that there is any scientific evidence to support the teaching of van Kessel et al. However, taken at face value, the basis of van Kessel et al. is the proposition that the binding of SAP to bacterial lipopolysaccharide, which is a toxic product, contributes to the pathology of illness caused by gram negative bacterial infection. Lipopolysaccharides (LPS) are also referred to as endotoxins. Van Kessel et al. teaches that SAP is capable of binding to endotoxin (col. 1, lines 47 to 49), and proposes that SAP can bind to LPS (endotoxin) and neutralize its biological activity (col. 3, lines 50 to 51). The reference hypothesizes that chronic bacterial infections and particularly LPS contribute to the development of Alzheimer's disease (col. 3, lines 60 to 64), and that SAP and fragments derived from SAP with a strong LPS-binding and neutralizing action can therefore be of importance in eliminating the part played by LPS in the development of Alzheimer's disease (col. 4, lines 39 to 43). Van Kessel et al. therefore proposes that SAP and/or fragments thereof should be administered to patients in order to treat or prevent Alzheimer's disease. The method taught by Van Kessel et al. would actually increase a patient's circulating SAP concentration, which is exactly the opposite of the effect of my invention. My invention produces immediate, profound depletion of virtually all the SAP from the circulation in order to provide therapeutic benefit to patients with amyloidosis of all types, and amyloid-associated diseases such as Alzheimer's disease.

(14) The official action stated that column 5, lines 1 to 20, of van Kessel et al. teaches to quantify the concentration of SAP. This is not correct. The cited passage in van Kessel et al. teaches that SAP and/or fragments thereof can also be used for the diagnosis of infection with gram negative bacteria or sepsis. It is the presence of endotoxin in blood or blood fractions such as serum or plasma which is being measured here. SAP is bound to a carrier such as a microtitre plate, column, membrane or beads (column 5, lines 19 and 20) and the endotoxin is assayed from the blood sample. Binding between endotoxin and SAP measured in order to quantify endotoxin in the blood, and not to quantify the concentration of SAP.

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(15) I conclude that van Kessel et al. teaches the opposite of my invention. While my invention teaches the depletion of SAP from circulation, van Kessel et al. teaches that SAP is therapeutic and should be increased in concentration in the blood. Monitoring circulating SAP is a part of the proper use of my invention to ensure that SAP depletion is taking place. On the other hand, van Kessel et al. uses SAP as a diagnostic reagent and monitors endotoxin concentration in the blood. Hertel et al. and van Kessel et al. are similarly directed to conflicting purposes - Hertel et al. teaches inhibiting SAP binding activity, whereas Van Kessel et al. teaches administering an LPS-binding form of SAP. Neither document described clearance of SAP from plasma or suggested monitoring SAP levels in plasma. Accordingly, I do not believe that one of ordinary skill in the art at the time the invention was made would have reasonably considered combining the teachings of Hertel et al and van Kessel et al. so as to obtain the claimed method of the '699 application. Furthermore, the cited references would not have provided one of ordinary skill in the art with any basis for having a reasonable expectation that the claimed method of the '699 application would operate successfully; *i.e.*, that SAP could be depleted from the plasma of a patient in need of such treatment by administration of the elected agent, and that the clearance of the SAP from the patient's plasma following such treatment could be successfully monitored.

(16) As stated above, my original invention for which a patent is sought is based on the discovery that the palindromic structure of (R)-1-[6-[(R)-2-Carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid enables this multi-ligand compound to cross link pairs of SAP molecules to form a novel molecular assembly that is recognized as abnormal by the body and immediately cleared from the circulating blood, leading to profound depletion of SAP, which is of therapeutic benefit in patients with all types of amyloidosis and amyloid-associated diseases. Prior to this discovery, there was no precedent for a small molecule drug that specifically targets a circulating plasma protein and causes its very rapid and profound clearance and depletion from the circulation. There is no prior art of any type that even remotely suggested this completely novel mechanism of drug action. The novel and non-obvious character of this new pharmacological mechanism of drug action are independently attested by Mr. Stu Borman and by Professor Leslie L. Iversen. Mr. Borman, a reviewer for *Chemical and Engineering News*, a journal of the American Chemical Society, identified my invention as one of the highlights in the field of medicinal chemistry for the

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year 2002 (*Chem. Eng. News*, 2002, 80:37-38). Professor Iversen is one of the world's most eminent neuropharmacologists, a Fellow of the Royal Society (the British National Academy of Science), and a member of the U.S. National Academy of Science. In addition to his outstanding academic career, during which he made enormous original contributions to understanding brain function, he was also for 11 years the Director of Neuroscience Drug Discovery for Merck, a leading U.S. pharmaceutical company which has a major research program in Alzheimer's disease and the related amyloid. He thus has uniquely extensive and detailed knowledge of drugs and drug actions in this field. In writing for *Nature*, one of the world's leading scientific journals, he described my work corresponding to the claimed invention as "a new pharmacological approach to treating human amyloid diseases;" and stated that "this new approach offers great promise for treating both peripheral amyloid disorders and possibly, Alzheimer's disease." (Iversen, "Amyloid diseases: Small drugs lead the attack," *Nature*, 2002, 414:231-233). Dr. Iversen clearly views my work as novel, original and surprising and in no way obvious or derivative. If this is the published opinion of a world leading authority, how can it be imagined that one of ordinary skill in the art would have found my invention to be obvious?

(17) I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and may jeopardize the validity of the application or any patent issued thereon.

MARK B. PEPYS

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Date

APPENDIX A

MARK BRIAN PEPYS

CURRICULUM VITAE

Name	MARK BRIAN PEPYS
Address	22 Wildwood Road, London NW11
Date of birth	18th September, 1944

Present appointment	Date of Appointment
Professor of Medicine and Head, Department of Medicine, Hampstead Campus, Royal Free and University College Medical School, University College London	01/10/99

MARK BRIAN PEPYS

University Education

Trinity College, Cambridge	1962-1965
University College Hospital Medical School	1965-1968

Degrees

B.A. (Hons.) (Cantab.) Natural Sciences Tripos:	Part I	Class I	1965
	Part II	Class I	
M.B., B.Chir. (Cantab.)			1968
M.A. (Cantab.)			1970
M.R.C.P. (U.K.)			1970
Ph.D. (Cantab.)	*"Role of complement in induction of the allergic response"*		1974
F.R.C.P.			1981
M.R.C.Path.			1981
M.D. (Cantab.)	*"Clinical and experimental studies of C-reactive protein and amyloid P component"*		1982
F.R.C.Path.			1991
F.R.S.			1998
F.Med.Sci.			1998

Academic distinctions

State Scholarship	1961

Trinity College, Cambridge:

Open Exhibition in Natural Sciences	1961
Preliminary Examination for Natural Sciences Tripos, Class I	1963
Preliminary Examination Prize	1963
Natural Sciences Tripos, Part I, Class I	1964
Senior Scholarship	1964
Natural Sciences Tripos, Part II (Pathology), Class I	1965
Tripos Examination Prize	1965
Research Scholarship	1970
Fellowship (Title A)	1973-1979

MARK BRIAN PEPYS

University College Hospital Medical School:

Filliter Entrance Scholarship in Pathology and Microbiology	1965
Trotter Medal for Clinical Surgery	1966
Alexander Bruce Gold Medal for Surgical Pathology	1967
Filliter Exhibition in Pathology and Microbiology	1967
Fellowes Gold Medal for Clinical Medicine	1967
Sir William Gowers Prize for Clinical Medicine	1967
Liston Gold Medal for Clinical Surgery	1967
Atchison Scholarship for "Clinical and Academic Attainment"	1968-1969

Royal College of Physicians:

Goulstonian lecturer *"C-reactive protein, amyloidosis and the acute phase response"*	1982
Lumleian lecturer *"C-reactive protein and amyloidosis: from proteins to drugs?"*	1998
Moxon Trust Medal	1999

Royal College of Pathologists:

Kohn lecturer *"Serum amyloid P component: molecular interactions and clinical applications"*	1991

Royal College of Surgeons of England:

Sir Arthur Sims Commonwealth Travelling Professorship	1991

Royal Society of London:

Fellow	1998

Academy of Medical Sciences:

Founder Fellow	1998

Renal Association:

Chandos lecturer *"Prognostic and pathogenetic significance of C-reactive protein"*	2000

MARK BRIAN PEPYS

British Society for Rheumatology:

Heberden medallist and orator
"Pentraxins in rheumatology: physiology, pathology and new drugs" 2002

University College London:

Fellow 2003

American Society of Nephrology:

State of the Art lecturer
"Recent advances in systemic amyloidosis" 2003

Israel Society for Rheumatology:

Gerald Loewi Memorial lecturer
"Amyloidosis and C-reactive protein: from old molecules to new drugs" 2004

Imperial College Faculty of Medicine:

Fellow 2004

Membership of Scientific and Medical Societies

Fellow of the Royal Society
Fellow of the Royal College of Physicians, London
Fellow of the Royal College of Pathologists
Founder Fellow of the Academy of Medical Sciences
Honorary Member of the Association of Physicians
Member Medical Research Society
British Society for Immunology
British Society for Allergy and Clinical Immunology
International Society for Amyloidosis
Antibody Club
Biochemical Society
British Society for Rheumatology
Molecular Medicine Society (Fellow)
Society for Neuroscience
American Association for the Advancement of Science
British Association

MARK BRIAN PEPYS

Membership of Academic Committees

University Grants Committee Equipment Sub-Committee	1989
Medical Research Council Systems Board Grants Committee B	1986-1990
Royal College of Physicians Specialist Committee on Clinical Immunology and Allergy	1988-1991
Royal Society Grants Committee F	1998-2001
Royal Society Sectional Committee 10	2001-2003
Medical Research Council Molecular and Cell Medicine Board	2000-2004
Royal Society Council	2003-2005
Academy of Medical Sciences Council	2004-2006

Membership of Editorial Boards

Journal of Immunological Methods	1975-1982
Clinical and Experimental Immunology	1980-1997
Clinical Allergy	1984-1988
Biochemical Journal, Editorial Adviser	1991-1998
Amyloid: Journal of Protein Folding Disorders	1994-

Previous appointments

House Physician to Medical Unit, University College Hospital, (Professor Lord Rosenheim, Professor C.E. Dent, FRS and Dr C.J. Dickinson)	1968-1969
House Surgeon to Surgical Unit, University College Hospital	1969
Senior House Officer to Dr D.K. Peters, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital	1969-1970
Research Assistant to Dr D.K. Peters, Honorary Medical Registrar, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital	1970
M.R.C. Junior Research Fellowship, Immunology Division (Professor R.R.A. Coombs, FRS), Department of Pathology, University of Cambridge	1970-1973
Research Scholar, Trinity College, Cambridge	1970-1973
Fellow, Trinity College, Cambridge	1973-1979
Medical Registrar to Professor C.C. Booth, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital	1973-1974

MARK BRIAN PEPYS

Previous appointments (cont)

Assistant Lecturer in Medicine, Honorary Senior Registrar to Professor C.C. Booth, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital	1974-1976
Senior Lecturer and Head of Immunology, Honorary Consultant, Royal Free Hospital School of Medicine	1976-1977
Senior Lecturer in Medicine, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital	1977-1980
Consultant Physician, Hammersmith Hospital, London	1977-1999
Reader in Immunological Medicine, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital	1980-1984
Group Leader, MRC Acute Phase Protein Research Group	1983-1988
Professor of Immunological Medicine, Department of Medicine, Royal Postgraduate Medical School, London	1984-1999
Assistant Director (Research), Department of Medicine, Royal Postgraduate Medical School, London	1987-1989
Research Coordinator to Hammersmith and Queen Charlotte's Special Health Authority	1988-1995

Research grants awarded

1975	Medical Research Council. *"Role of lymphocytes and complement in immunological function of the intestine"* £40,000 over 4 years
1977	Medical Research Council. *"Identification and absolute enumeration of lymphocyte populations in whole blood and tissue sections"* £33,000 over 3 years
1977	Medical Research Council. *"Role of complement in the induction of antibody formation in human and murine systems"* £33,000 over 3 years
1977	Medical Research Council. *"Immunological mechanisms underlying the acute and chronic relapsing forms of experimental allergic neuritis"* £34,000 over 3 years (with Professor P.K. Thomas)

MARK BRIAN PEPYS

Research grants awarded (cont)

1977	Wellcome Trust. *"Investigation of possible immunological factor in epilepsy"* £20,000 over 2 years (with Professor G. Ettlinger)
1978	Wellcome Trust. *"Role of C-reactive protein in immunological responses"* £25,000 over 3 years
1978	National Kidney Research Fund. *"C-reactive and amyloid P proteins in renal disease"* £15,000 over 2 years
1979	Medical Research Council. Programme Grant. *"Biological and clinical studies of C-reactive protein and serum amyloid P component"* £240,000 over 5 years
1979	Fisons Limited. *"Therapeutic trial of absorbable cromone in Crohn's disease"* £17,000 over 2 years (with Dr V.S. Chadwick)
1980	Leukaemia Research Fund. *"Characterisation by surface markers and enumeration of leukaemic cells in whole blood using monoclonal antibodies and alkaline phosphatase labelled reagents: a method for routine clinical use"* £35,000 over 3 years
1981	Medical Research Council Training Fellowship for Dr I.F. Rowe £30,000 over 3 years
1981	Cancer Research Campaign. *"Role of the interaction between fibronectin and amyloid P component in cell-substratum interactions of normal and malignant cells"* £25,000 over 2 years
1982	Medical Research Council Training Fellowship for Dr C.R.K. Hind £33,000 over 3 years
1983	Medical Research Council. Programme Grant. Renewed for 1984-1989 £302,000 over 5 years

MARK BRIAN PEPYS

Research grants awarded (cont)

1983	Medical Research Council. Group status awarded and designated as the MRC Acute Phase Protein Research Group £78,315 over 5 years
1986	Medical Research Council Training Fellowship for Dr P.N. Hawkins £45,000 over 3 years
1986	Medical Research Council. *"The three-dimensional structure analysis of pentraxins: biochemical and X-ray studies of serum amyloid P component"* £52,000 over 3 years (with Dr S.P. Wood and Professor T.L. Blundell)
1987	Medical Research Council. *"$\beta_{\square}$-Microglobulin derived amyloidosis in haemodialysis and CAPD: precursor protein clearance and amyloidogenesis"* £46,000 over 2 years (with Dr F.W. Ballardie and Professor D.N.S. Kerr)
1987	Medical Research Council. *"Structural studies of amyloid fibril proteins and their precursors"* £44,000 over 3 years
1988	Arthritis and Rheumatism Council. *"Molecular, biological and clinical studies of pentraxin-chromatin interactions"* £52,680 over 3 years
1989	Medical Research Council. *"Characterisation of amyloid fibril-associated glycosaminoglycans"* £19,922 over 1 year
1989	Wellcome Trust. *"Localisation of serum amyloid P component in joints in vivo: mechanisms and significance"* £96,500 over 2 years
1989	Medical Research Council. Programme Grant. *"Structural, functional and clinical studies of the pentraxins and amyloidosis"* Renewed for 1989-1994 £532,600 over 5 years

MARK BRIAN PEPYS

Research grants awarded (cont)

1989 Medical Research Council. *"Three dimensional structure analysis of pentraxins: X-ray studies of ligand binding to serum amyloid P component"*
£87,300 over 3 years (with Professor T.L. Blundell and Dr S.P. Wood)

1989 Horserace Betting Levy Board. *"Development of an equine acute phase protein test for diagnosis"*
£44,830 over 3 years

1990 Medical Research Council. *"In vivo distribution, clearance and metabolism of C-reactive protein in man in health and disease"*
£100,500 over 3 years (with Dr P.N. Hawkins)

1991 Medical Research Council. Supplement to Programme Grant. 1990-1994
£108,000 over 4 years

1991 Medical Research Council. *"Characterisation of apoA-I mutations and mechanisms of amyloidogenesis in familial systemic Ostertag-type amyloidosis"*
£75,000 over 2 years (with Dr A.K. Soutar and Dr P.N. Hawkins)

1991 The Maurice Wohl Charitable Foundation
£90,000 towards building of new laboratories

1993 Medical Research Council. *"Expression, structure and properties of the human lysozyme variants Thr56 and His67. A new model of amyloidogenesis"*
£90,613 over 2 years (with Dr A.K. Soutar)

1993 Medical Research Council
Training Fellowship for Dr L.B. Lovat
£82,500 over 3 years

1994 Wellcome Trust. *"Biomedical applications of mass spectrometry"*
£312,369 (with Dr G.W. Taylor, Professor D.S. Davies and Professor R.I. Lechler)

MARK BRIAN PEPYS

Research grants awarded (cont)

1994 Medical Research Council. Programme Grant. *"Structural, functional and clinical studies of the pentraxins and amyloidosis"*
Renewed for 1994-1999
£2,035,148 over 5 years (with Dr P.N. Hawkins)

1994 Medical Research Council. *"Structure and ligand binding of serum amyloid P component"*
£134,858 over 3 years (with Dr S.P. Wood and Dr I.J. Tickle)

1995 Arthritis and Rheumatism Council
Clinical Research Fellowship for Dr M.C.M. Bickerstaff
£119,717 over 3 years (with Professor M.J. Walport)

1996 Medical Research Council. Supplement to Programme Grant 1996-1999
£148,584 over 3 years (with Dr P.N. Hawkins)

1996 F. Hoffmann-La Roche Ltd. *"Studies of serum amyloid P component in amyloidosis"*
£302,000 for equipment

1996 The Wellcome Trust. University Award for Dr P.N. Hawkins
"Diagnostic, pathogenetic and therapeutic studies in amyloidosis"
£205,412 over 3 years

1996 The Maurice Wohl Charitable Foundation
£22,000 towards purchase of equipment

1997 The Wellcome Trust. *"Ligand recognition and structure-function relationships in human C-reactive protein"*
£166,030 over 3 years (with Dr S.P. Wood)

1997 F. Hoffmann-La Roche Ltd. *"Studies of serum amyloid P component in amyloidosis"*
£105,000 over 1 year

1998 Joint Medical Research Council and Department of Health Transmissible Spongiform Encephalopathies Initiative. *"Do scrapie and Creutzfeldt-Jakob disease develop normally in mice with targeted deletion of the serum amyloid P component gene?"*
£315,482 over 3 years (with Professor J. Collinge, Dr M.E. Bruce and Ms P.A. McBride)

MARK BRIAN PEPYS

Research grants awarded (cont)

1998	Medical Research Council Clinical Training Fellowship for Dr M. Noursadeghi £108,800 over 3 years (with Professor J. Cohen)
1999	The Wellcome Trust Research Training Fellowship for Dr J.D. Gillmore £151,974 over 3 years
1999	Medical Research Council. Programme Grant. *"Pentraxins and amyloidosis: Functions and clinical significance"* Renewed for 1999-2004 £2,362,180 over 5 years (with Professor P.N. Hawkins)
2000	British Heart Foundation. *"The diagnostic and prognostic significance of inflammation and the possession of certain vascular and inflammatory polymorphisms in coronary in-stent restenosis"* £131,592 over 2 years (with Dr K.M. Fox and Professor S. Humphries)
2000	Medical Research Council, Development Grant *"Structural analysis of ligand recognition and associated biological roles of pentraxins"* £227,474 over 3 years (with Professor S.P. Wood)
2000	Medical Research Council Clinical Training Fellowship for Dr G.M. Hirschfield £112,753 over 3 years
2001	Supplement and extension to Joint Medical Research Council and Department of Health Transmissible Spongiform Encephalopathies Initiative. *"Do scrapie and Creutzfeldt-Jakob disease develop normally in mice with targeted deletion of the serum amyloid P component gene?"* £60,636 over 18 months (with Professor J. Collinge, Dr M.E. Bruce and Ms P.A. McBride)
2002	The Wolfson Foundation, Equipment Grant *"Molecules to medicines at the Royal Free"* £1,500,000 (with Dr J.J. Hsuan)
2004	British Heart Foundation PhD Studentship for Ms H. Mikolajek £68,208 over 3 years (with Professor S.P. Wood)

Research grants awarded (cont)

2004 Medical Research Council. Programme Grant. *"Pentraxins and amyloidosis: From molecular mechanisms to medicines"*
Renewed for 2004-2009
£1,800,016 over 5 years (with Professor P.N. Hawkins)

2004 National Institutes of Health
"Targeting C-reactive protein in atherothrombotic disease"
$861,200 over 4 years

PUBLICATIONS

I. ORIGINAL PAPERS

A. Complement and induction of immunological responses

1. Pepys, M.B. (1972) Role of complement in induction of the allergic response. *Nature New Biol.*, **237:** 157-159.

2. Janossy, G., Humphrey, J.H., Pepys, M.B. and Greaves, M.F. (1973) Complement independence of stimulation of mouse splenic B lymphocytes by mitogens. *Nature New Biol.*, **245:** 108-112.

3. Pepys, M.B. (1974) Complement-mediated mixed aggregation of murine spleen cells. *Nature,* **249:** 51-53.

4. Feldmann, M. and Pepys, M.B. (1974) Role of C3 in *in vitro* lymphocyte cooperation. *Nature,* **249:** 159-161.

5. Pepys, M.B. and Taussig, M.J. (1974) Complement-independence of tolerance induction. *Eur. J. Immunol.*, **4:** 349-352.

6. Pepys, M.B. (1974) Role of complement in induction of antibody production *in vivo.* Effect of cobra factor and other C3-reactive agents on thymus-dependent and thymus-independent antibody responses. *J. Exp. Med.*, **140:** 126-145.

7. Pepys, M.B. and Butterworth, A.E. (1974) Inhibition by C3 fragments of C3-dependent rosette formation and antigen-induced lymphocyte transformation. *Clin. Exp. Immunol.*, **18:** 273-282.

8. Pepys, M.B. (1975) Studies *in vivo* of cobra factor and murine C3. *Immunology,* **28:** 369-377.

9. Pepys, M.B. and Wilson, D.V. (1975) A new immunoassay for C3. Application of the cell-linked antigen radioactive antibody (CLARA) technique. *J. Immunol. Methods,* **6:** 225-233.

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B. C-reactive protein, amyloid P component and the acute phase response

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II. CHAPTERS, REVIEWS AND REPORTS

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IV. PATENT

1. Therapeutic and Diagnostic Agents for Amyloidosis. Freemedic PLC, M.B. Pepys and T.L. Blundell. US Patent No. 6,126,918 issued 3 October 2000.

Our Ref: 206002/JND/SV

Your Ref: 068800-0284057

Dr Tom Cawley
Pillsbury Winthrop LLP
1600 Tyson Boulevard
McLean, Virginia 22102,
USA

BY EMAIL AND MAIL

Dear Tom,

US Patent Application No. 09/985,699
Therapeutic Protein Depletion

Thank you for your letter of 9th March 2005 reporting the issuance of a US Office Action to which a response is due by **18th May 2005**. Please prepare and file a response in time to meet the due date.

You have suggested that we submit a Declaration signed by Professor Pepys to deal with the obviousness objections raised by the Examiner. Accordingly, we are attaching a draft of a Declaration for this purpose. Please review the Declaration and put it into a form suitable for use under your practice. If you believe that the Declaration should be amended in order to deal with the objections of this particular Examiner, please feel free to make suggestions for amendment.

Our understanding is that the Examiner is requiring a restriction of the claims to the subject-matter of present claim 20 in which the disease associated protein of present claim 18 is specified as SAP. We understand that a more generic invention could be made the subject of a divisional application at a later date.

The Examiner has cited the references of Hertel and van Kessel against the restrictive claim. The essence of the Examiner's objection appears to be that the skilled addressee could modify the teaching of Hertel in line with van Kessel to arrive obviously at the present invention. The Examiner appears to believe that the only distinguishing feature of the present claim over Hertel is the final step measuring the clearance of SAP. The Examiner asserts that van Kessel supplies this missing feature.

As currently framed, the Declaration makes the following points:

1) Hertel only suggests generically administration of D-prolines for treating diseases associated with amyloidosis. No compounds are actually administered. In fact, no compounds are even tested *in vitro*.

2) Hertel is exclusively concerned with inhibitors of SAP binding to amyloid fibrils.

3) Hertel describes the synthesis of very many compounds in 104 different examples. Whilst a shorter list of compounds is presented in columns 5 and 6, no specific compounds are tested *in vivo* or *in vitro*. Therefore, the skilled addressee would have to make a selection even to arrive at the compound of the present claim.

4) The present invention requires clearance of SAP and Hertel does not teach this. The present invention does not require inhibition of SAP binding to amyloid fibrils.

5) Hertel actually teaches that SAP is extremely stable outside the liver and that this arguably teaches away from expecting clearance of SAP.

6) Van Kessel teaches the use of SAP as a therapeutic (Professor Pepys strongly views this as scientifically incorrect). Use as a therapeutic would increase circulating SAP concentration, which is the opposite of the present invention.

7) Van Kessel uses SAP to quantify endotoxin in the blood (*i.e.* SAP is used as a diagnostic reagent). Quantification of SAP in the blood is not measured by van Kessel.

8) It makes no sense to combine Hertel and Van Kessel. Even if you did, neither document describes clearance of SAP from plasma or monitoring of SAP levels in plasma.

9) The present invention is unprecedented and has been hailed as a highly significant achievement by both a world authority on neuropharmacology and a reviewer for the American Chemical Society.

I look forward to receiving a draft of your proposed submission to the USPTO. As always, feel free to call if you wish to discuss any of this.

Best wishes.
Yours sincerely

J N Daniels

Enc: Draft Declaration

Our Ref: 206002/JND/SV

Your Ref: 068800-0284057

Dr Tom Cawley
Pillsbury Winthrop LLP
1600 Tyson Boulevard
McLean, Virginia 22102,
USA

BY EMAIL AND MAIL

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I look forward to receiving a draft of your proposed submission to the USPTO. As always, feel free to call if you wish to discuss any of this.

Best wishes.
Yours sincerely

J N Daniels

Enc: Draft Declaration

I, Mark B Pepys, hereby declare the following:

(1) I am Professor of Medicine and Head, Department of Medicine, Hampstead Campus, Royal Free and University College Medical School. Further details of my educational qualifications and a list of publications are set out on the attached CV. I have been working on serum amyloid P component (SAP) for 30 years.

(2) I am the sole inventor for the present US Patent Application No. 09/985,699 directed to "Therapeutic Agents".

(3) My invention is directed to a method for the depletion of a disease-associated protein population from the plasma of a subject in need of such treatment, which comprises:

(a) administering to the subject a therapeutically effective amount of a non-proteinaceous agent, which agent comprises a plurality of ligands covalently co-linked to permit complexation with a plurality of the disease-associated proteins in the presence thereof, wherein at least two of the ligands are the same or different and are capable of being bound by ligand binding sites present on the proteins;

(b) binding of at least two of the ligands by the ligand binding sites of the proteins in the plasma;

(c) forming thereby a complex between the agent and a plurality of the proteins, wherein the complex is abnormal to the subject; and

(d) causing the complex to be identified by the physiological mechanisms of the subject and cleared from the plasma; and

(e) monitoring the clearance of the disease-associated protein population from the subject's plasma.

The non-proteinaceous agent is (R)-1-[6-(R)-2-Carboxypyrrolidin-l-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid or a pharmaceutically acceptable salt or mono- or diester thereof and the disease associated protein is SAP.

(4) I have read and am familiar with the Office Action dated 18th February 2005 from the US Patent and Trademark Office, together with the two cited references of Hertel *et al* (US6103910) and van Kessel *et al* (US6365570). I understand that an

obviousness rejection has been made in the Office Action in view of these two references. I strongly believe that neither Hertel nor van Kessel make my invention obvious to one skilled in the art and explain below my reasons for reaching this conclusion.

(5) Hertel discloses that her invention relates to D-prolines of the general formula I-A or I-B (column 1, lines 30 to 45). These are general formulae for D-prolines and are limited only by the identity of the functional groups as set out in the section bridging column 1 to column 2, line 48. These compounds are generally defined, not specifically defined. Hertel *et al* then make a number of statements relating to these generally-defined D-prolines.

> "A method of using these compounds for treating diseases associated with amyloidosis by administering to a subject in need of such treatment an effective amount of one of the above-identified compounds ... is also provided". (Column 2, lines 50 to 56).
>
> "For therapy pharmaceutically active compounds have to be found which would prevent the interaction of SAP with amyloid fibrils" (Column 4, lines 27 to 29).
>
> "SAP is a calcium-dependent ligand binding protein. It is produced and degraded exclusively in hepatocytes and extremely stabile [sic] outside the liver" (Column 4, lines 36 to 38).
>
> "The participation of SAP in the pathogenesis of amyloidosis *in vivo* confirms that inhibition of binding to amyloid fibrils is an attractive therapeutic target in a range of serious human diseases" (Column 4, lines 39 to 42).

(6) These statements mean that Hertel is interested in compounds that interfere with binding of SAP to amyloid fibrils that may be useful for therapy of amyloidosis and diseases, such as Alzheimer's disease, that are associated with amyloidosis. Hertel is therefore only concerned with inhibitors of SAP binding to amyloid fibrils.

(7) Hertel does not teach the skilled reader anything further about the administration of D-prolines because no *in vivo* experiments or trials are described. All that can be inferred from the passages quoted above is that the generically-described D-prolines might be useful as inhibitors of SAP binding to amyloid fibrils. Nothing is taught about the efficacy of the compounds in general as inhibitors *in vitro* or *in vivo*.

(8) In the next part of the Hertel specification from column 5 onwards, a very large number of specific compounds of formulae I-A and I-B are described. A list of compounds is presented in columns 5 and 6 and later there are presented 104 different examples of the synthesis of compounds according to formulae I-A and I-B. Examples A, B and C are directed to examples of tablets or capsules using an unnamed active ingredient. None of the specific compounds is described as being tested by Hertel for their ability to inhibit binding of SAP to amyloid fibrils either *in vitro* or *in vivo*. Nothing can be inferred from the Hertel disclosure as to which of the specific compounds might be selected for use as an inhibitor.

(9) I disagree with the conclusion reached by the Examiner that "Hertel teaches to administer the claimed compound of claim 20 (the elected agent) to a patient for treating diseases associated with amyloidosis such as Alzheimer's disease". This is wholly incorrect. Hertel does not describe the administration of any specific compound to a patient. The claimed compound of present claim 20 is one of very many compounds specified in Hertel. The skilled reader would first have to select such a compound for administration. Hertel describes no distinction between compounds disclosed because none has been tested. The skilled reader cannot therefore infer anything about the efficacy of compounds as inhibitors of SAP binding to amyloid fibrils until at least *in vitro* testing has been carried out. Moreover, the therapeutic efficacy of such a compound could not be inferred without suitable *in vivo* trials.

(10) There is, however, an even more fundamental distinction between my invention and the subject-matter of Hertel. There is no mention of any of the critical

components of my invention; namely, the requirement for a palindromic structure of the ligand drug, the requirement that it cross-link pairs of SAP molecules to form a complex abnormal to the subject and the causing of clearance of the cross-linked SAP from the blood, as demonstrated by measurement of serum or plasma SAP concentration so as to provide a therapeutic benefit. My invention does not require inhibition of SAP binding to amyloid fibrils, as described in Hertel.

(11) Hertel suggests only that generically-disclosed D-prolines may act as inhibitors of the interaction between SAP and amyloid fibrils. There is no disclosure or suggestion of the characteristics of my invention, as described above. There is, in fact, no mention at all in Hertel of clearance of SAP from plasma. Clearance is neither predicted by Hertel nor measured. Even if one of Hertel's compounds had been selected and found to be effective as an inhibitor of the interaction between the SAP and amyloid fibrils, this would teach nothing about the ability of that compound to clear SAP from the plasma of a subject.

(12) In fact, the skilled reader would be taught the opposite. Hertel teaches that SAP is extremely stable outside the liver (column 4, line 38). This teaches that SAP would be expected to be stable in the plasma and so clearance would not be expected.

(13) I therefore conclude that Hertel does not teach anything about the activity of the compounds disclosed other than a suggestion that the disclosed D-prolines generically might act as inhibitors of SAP binding to amyloid fibrils. Clearance of SAP from plasma is neither disclosed nor suggested. The efficacy of any of the compounds of Hertel is not revealed because no experiments administering the compounds to a subject are described.

(14) Van Kessel *et al* describe possible uses of SAP and fragments of SAP totally unrelated to anything in my invention. I do not believe that there is any scientific evidence to support the teaching of van Kessel. However, taken at face value, the basis of van Kessel is the binding of SAP to bacterial lipopolysaccharide (LPS), which is a toxic product that contributes to the pathology of illness caused by gram negative bacterial infection. Lipopolysaccharides are also referred to as endotoxins.

Van Kessel teaches at column 1, lines 47 to 49 that SAP is capable of binding to endotoxin. Van Kessel proposes at column 3, lines 50 to 51 that SAP binds to LPS (endotoxin) and is capable of neutralising its biological activity. Van Kessel hypothesises at lines 60 to 64 that chronic bacterial infections and particularly LPS contribute to the development of Alzheimer's disease. In column 4, lines 39 to 43, van Kessel teaches that SAP and fragments derived from SAP with a strong LPS-binding and neutralising action can therefore be of importance in eliminating the part played by LPS in the development of Alzheimer's disease. Van Kessel therefore proposes the use of SAP and/or fragments thereof for the manufacture of a pharmaceutical composition for the therapeutic and preventive treatment of Alzheimer's disease.

(15) This is the complete opposite of my invention. My invention produces immediate, profound depletion of virtually all the SAP from the circulation in order to effect therapeutic benefit in patients with amyloidosis of all types and amyloid-associated diseases such as Alzheimer's disease. In contrast, van Kessel teaches that SAP or fragments should be administered to patients with Alzheimer's disease. This would actually increase a patient's circulating SAP concentration – exactly the opposite of the effect of my invention.

(16) The Examiner has cited column 5, lines 1 to 20 of van Kessel suggesting that this teaches to quantify the concentration of SAP. This is not correct. This passage in van Kessel teaches that SAP and/or fragments thereof can also be used for the diagnosis of infection with gram negative bacteria or sepsis. It is the presence of endotoxin in blood or blood fractions such as serum or plasma which is being measured here. SAP is bound to a carrier such as a microtitre plate, column, membrane or beads (column 5, lines 19 and 20) and the endotoxin is assayed from the blood sample. The measurement of binding between endotoxin and SAP is made to quantify endotoxin in the blood and not to quantify the concentration of SAP.

(17) I conclude that van Kessel teaches the opposite of my invention. Whilst my invention teaches the depletion of SAP from circulation, van Kessel teaches that SAP is therapeutic and should be increased in concentration in the blood. Monitoring

circulating SAP is a part of the proper use of my invention to ensure that SAP depletion is taking place. On the other hand, van Kessel monitors endotoxin concentration in the blood using SAP as a diagnostic reagent.

(18) I do not believe it is reasonable to combine the teachings of Hertel and van Kessel. Hertel teaches the use of generic D-prolines as possible inhibitors of the interaction between SAP and amyloid fibrils. Van Kessel is not concerned with D-prolines. Van Kessel is concerned with using SAP as a therapeutic, rather than its inhibition. Neither document describes clearance of SAP from plasma. Neither document describes the monitoring of SAP levels in plasma.

(19) My original invention that we seek to patent is that (R)-1-[6-[(R)-2-Carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid, which is a specific ligand bound by SAP, has a palindromic structure that enables it to cross link pairs of SAP molecules to form a novel molecular assembly that is recognised as abnormal by the body and immediately cleared from the circulating blood leading to profound depletion of SAP which is of therapeutic benefit in patients with all types of amyloidosis and amyloid-associated diseases.

(20) There is no precedent for a small molecule drug that specifically targets a circulating plasma protein and causes its very rapid and profound clearance and depletion from the circulation. There is no prior art of any type that even remotely suggests this completely novel mechanism of drug action. My invention of this new pharmacological mechanism of drug action is independently attested by Professor Leslie L Iversen and S. Borman. They make it absolutely clear that my invention is surprising, novel and in no way obvious. Professor Iversen is not simply someone of ordinary skill in the art. He is one of the most eminent neuropharmacologists in the world, a Fellow of the Royal Society (the British National Academy of Science) and a member of the US National Academy of Science. In addition to his outstanding academic career, during which he made enormous original contributions to understanding brain function, he was also for 11 years the Director of Neuroscience Drug Discovery for Merck, the leading US pharmaceutical company, with a major programme in Alzheimer's disease and the related amyloid. He thus has uniquely

extensive and detailed knowledge of drugs and drug actions in this field. In writing about my invention for *Nature*, the world's leading scientific journal, he makes it clear that my work is novel, original and surprising and in no way obvious or derivative (Nature, 2002, 414:231-232). If this is the published opinion of a world leading authority, how can it be imagined that one of ordinary skill in the art would have found my invention to be obvious? Borman, reviewing the medicinal chemistry highlights of the year for a journal of the American Chemical Society, identifies my invention as one of these highlights in view of its surprising novelty, not suggested by any previous work (Chem.Eng. News, 2002, 80:37-38)

I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the Unites States Code and that such wilful false statements may jeopardise the validity of the captioned application or any patent issued thereon.

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MARK B PEPYS

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Date